10/632,187

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E1            1     PERIFOROSIDE I/CN
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E3            0 --> PERIFOSIN/CN
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E5            1     PERIFUNAL/CN
E6            1     PERIGEN/CN
E7            1     PERIGEN W/CN
E8            1     PERIGRAN/CN
E9            1     PERIGULOSIDE/CN
E10           1     PERILAN RFC/CN
E11           1     PERILAX/CN
E12           1     PERILIPIN (HUMAN CLONE MGC:33812 IMAGE:5284402)/CN

=> s e4
L1            1 PERIFOSINE/CN

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   157716-52-4  REGISTRY
CN   Piperidinium, 4-[[hydroxy(octadecyloxy)phosphinyl]oxy]-1,1-dimethyl-,
     inner salt (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   D 21266
CN   NSC 639966
CN   Perifosine
FS   3D CONCORD
MF   C25 H52 N O4 P
SR   CA
LC   STN Files:  ADISINSIGHT, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB,
       CIN, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSRESEARCH, IPA, PHAR, PROMT,
       PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
DT.CA  CAplus document type:  Journal; Patent
RL.P   Roles from patents:  BIOL (Biological study); PREP (Preparation); USES
       (Uses)
RLD.P  Roles for non-specific derivatives from patents:  BIOL (Biological
       study); PREP (Preparation); USES (Uses)
RL.NP  Roles from non-patents:  ANST (Analytical study); BIOL (Biological
       study); PROC (Process); PRP (Properties); USES (Uses)
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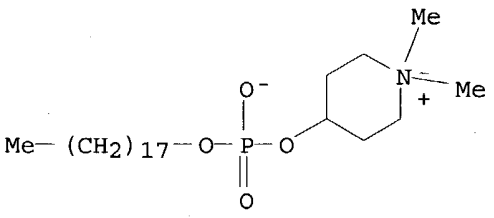


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DELACROIX

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=> e miltefosine/cn
E1            1     MILTAUN/CN
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E3            1 --> MILTEFOSINE/CN
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E5            1     MILTEMP/CN
E6            1     MILTEX/CN
E7            1     MILTHANTHINE/CN
E8            1     MILTIODIOL/CN
E9            1     MILTIONONE I/CN
E10           1     MILTIONONE II/CN
E11           1     MILTIPOLONE/CN
E12           1     MILTIRON/CN

=> s e3
L2            1 MILTEFOSINE/CN

=> d l2 1

L2   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   58066-85-6  REGISTRY
CN   Ethanaminium, 2-[[(hexadecyloxy)hydroxyphosphinyl]oxy]-N,N,N-trimethyl-,
     inner salt (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Choline phosphate, hexadecyl ester, hydroxide, inner salt (6CI)
OTHER NAMES:
CN   D 18506
CN   FOS-Choline 16
CN   Hexadecylphosphocholine
CN   Hexadecylphosphorylcholine
CN   HPC
CN   Miltefosine
CN   Miltex
CN   n-Hexadecylphosphocholine
CN   n-Hexadecylphosphorylcholine
CN   NSC 605583
FS   3D CONCORD
DR   93597-88-7
MF   C21 H46 N O4 P
CI   COM
LC   STN Files:   ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
       BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT,
       CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS,
       IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, PS, RTECS*,
       SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   WHO
DT.CA  CAplus document type:  Conference; Dissertation; Journal; Patent
RL.P   Roles from patents:  BIOL (Biological study); PREP (Preparation); PROC
       (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P  Roles for non-specific derivatives from patents:  BIOL (Biological
       study); USES (Uses)
RL.NP  Roles from non-patents:  ANST (Analytical study); BIOL (Biological
       study); PREP (Preparation); PROC (Process); PRP (Properties); RACT
       (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents:  BIOL (Biological
       study); PREP (Preparation); USES (Uses)
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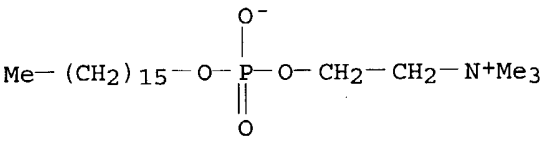

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
385 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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=> e hexadecylphosphocholine/cn
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E2            1     HEXADECYLPHOSPHINE/CN
E3            1 --> HEXADECYLPHOSPHOCHOLINE/CN
E4            1     HEXADECYLPHOSPHONIC ACID/CN
E5            1     HEXADECYLPHOSPHORYLCHOLINE/CN
E6            1     HEXADECYLPOLY(ETHYLENEOXY)ETHANOL/CN
E7            1     HEXADECYLPOLY(ETHYLENEOXY)ETHYL METHACRYLATE/CN
E8            1     HEXADECYLPYRIDINE BROMIDE/CN
E9            1     HEXADECYLPYRIDINIUM/CN
E10           1     HEXADECYLPYRIDINIUM BROMIDE/CN
E11           1     HEXADECYLPYRIDINIUM CARBONATE/CN
E12           1     HEXADECYLPYRIDINIUM CHLORANILATE/CN

=> s e3
L3            1 HEXADECYLPHOSPHOCHOLINE/CN

=> d l3 1

L3   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   58066-85-6  REGISTRY
CN   Ethanaminium, 2-[[(hexadecyloxy)hydroxyphosphinyl]oxy]-N,N,N-trimethyl-,
     inner salt (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Choline phosphate, hexadecyl ester, hydroxide, inner salt (6CI)
OTHER NAMES:
CN   D 18506
CN   FOS-Choline 16
CN   Hexadecylphosphocholine
CN   Hexadecylphosphorylcholine
CN   HPC
CN   Miltefosine
CN   Miltex
CN   n-Hexadecylphosphocholine
CN   n-Hexadecylphosphorylcholine
CN   NSC 605583
FS   3D CONCORD
DR   93597-88-7
MF   C21 H46 N O4 P
CI   COM
LC   STN Files:   ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
       BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT,
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CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

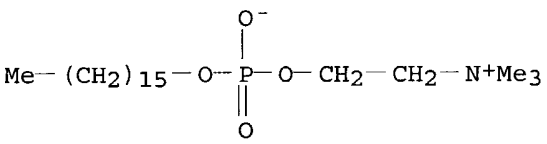
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent

RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

384 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
385 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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=> d l6 que stat;fil medline,hcaplus,embase,biosis;s l6
L4                STR
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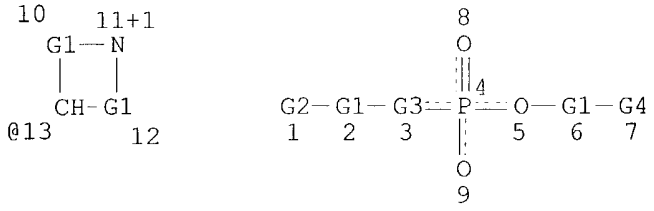

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NODE ATTRIBUTES:
CHARGE  IS E+1     AT  11
CHARGE  IS E+1     AT  14
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  14

STEREO ATTRIBUTES: NONE
L6         12775 SEA FILE=REGISTRY SSS FUL L4

100.0% PROCESSED 333110 ITERATIONS                      12775 ANSWERS
SEARCH TIME: 00.00.38



COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               162.14     165.29

FILE 'MEDLINE' ENTERED AT 15:50:16 ON 22 SEP 2004

FILE 'HCAPLUS' ENTERED AT 15:50:16 ON 22 SEP 2004
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TOO MANY TERMS FOR FILE CROSSOVER IN L6
There are limits on the size of an answer set being crossed over from
one file to another.  Enter HELP CROSSOVER at an arrow prompt (=>)
for specific information.


Searched by: Mary Hale 571-272-2507 REM 1D86
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COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         4.81     170.10

FILE 'REGISTRY' ENTERED AT 15:50:26 ON 22 SEP 2004
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provided by InfoChem.

STRUCTURE FILE UPDATES:   21 SEP 2004  HIGHEST RN 749178-43-6
DICTIONARY FILE UPDATES:  21 SEP 2004  HIGHEST RN 749178-43-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> s l6 or l6
L7       12775 L6 OR L6

=> d 9000 rn

L7   ANSWER 9000 OF 12775  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   111621-46-6  REGISTRY


=> s l7 range=(111621-46-6,)
L8        9000 L6 OR L6

=> d 12775 rn l7

L7   ANSWER 12775 OF 12775  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   63-89-8  REGISTRY


=> s l7 range=(63-89-8,111621-46-6)
L9        3776 L6 OR L6

=> s l7 range=(,63-89-8)
L10          1 L6 OR L6

=> fil medline,hcaplus,embase,biosis;s l8 or l9 or l10
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
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FULL ESTIMATED COST                                         1.64     171.74

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FILE 'HCAPLUS' ENTERED AT 15:52:18 ON 22 SEP 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


Searched by: Mary Hale 571-272-2507 REM 1D86
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FILE 'BIOSIS' ENTERED AT 15:52:18 ON 22 SEP 2004

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=> s l8 or l9 or l10
L11 8972 FILE MEDLINE
L12 28853 FILE HCAPLUS
L13 16218 FILE EMBASE
L14 13299 FILE BIOSIS

TOTAL FOR ALL FILES
L15 67342 L8 OR L9 OR L10

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L16 785 FILE MEDLINE
L17 2065 FILE HCAPLUS
L18 1351 FILE EMBASE
L19 1211 FILE BIOSIS

TOTAL FOR ALL FILES
L20 5412 L15 AND (TUMOUR? OR TUMOR? OR NEOPLASM? OR ONCOS? OR CANCER OR CARCINOMA? OR MALIGNAN? OR BENIGN OR ANTITUMOR OR ANTITUMOUR)

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L21 15 FILE MEDLINE
L22 17 FILE HCAPLUS
L23 22 FILE EMBASE
L24 28 FILE BIOSIS

TOTAL FOR ALL FILES
L25 82 L20 AND (ENGEL, J? OR GUNTHER, E? OR SINDERMANN, H?)/AU

=> dup rem l25
PROCESSING COMPLETED FOR L25
L26 47 DUP REM L25 (35 DUPLICATES REMOVED)

=> d 1-47 cbib abs;s engel, j?/au;s gunther, e?/au;s sindermann, h?/au

L26 ANSWER 1 OF 47 HCAPLUS COPYRIGHT 2004 ACS on STN
2004:120730 Document No. 140:157434 Use of alkyl phosphocholines in combination with **antitumor** medicaments for the treatment of **benign** and **malignant tumors**. **Engel, Jurgen; Gunther, Eckhard; Sindermann, Herbert** (Zentaris GmbH, Germany). PCT Int. Appl. WO 2004012744 A1 20040212, 21 pp. DESIGNATED STATES: W: AU, BR, BY, CA, CN, CO, GE, HR, ID, IL, IN, IS, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PH, PL, RU, SG, UA, UZ, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2003-EP8346 20030729. PRIORITY: US 2002-PV399615 20020730.
AB The invention discloses the use of alkyl phosphocholines in combination with **antitumor** medicaments for treating **benign** and

Searched by: Mary Hale 571-272-2507 REM 1D86

malignant tumor diseases in humans and mammals. The alkyl phosphocholines can be used in combination with one or a combination of several approved cytostatics. Compds. of the invention include e.g. perifosine.

L26 ANSWER 2 OF 47 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
2001:196351 Document No. 135:161991 Perifosine: oncolytic, ether phospholipid. **Engel, J.**; Hilgard, P.; Klenner, T.; Kutscher, B.; Nossner, G.; Traiser, M.; Voss, V. (ASTA Medica AG, Frankfurt, 60314, Germany). Drugs of the Future, 25(12), 1257-1260 (English) 2000. CODEN: DRFUD4. ISSN: 0377-8282. Publisher: Prous Science.
AB A review with 21 refs. regarding the oncolytic drug perifosine. Topics discussed include its synthesis, pharmacol. actions, pharmacokinetics, toxicol., and clin. studies.

L26 ANSWER 3 OF 47 MEDLINE on STN DUPLICATE 2
2001123772. PubMed ID: 11142690. Phase II study of miltefosine 6% solution as topical treatment of skin metastases in breast **cancer** patients. Smorenburg C H; Seynaeve C; Bontenbal M; Planting A S; **Sindermann H**; Verweij J. (Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital Rotterdam, The Netherlands.. smorenburg@vvdh.azr.nl) . Anti-cancer drugs, (2000 Nov) 11 (10) 825-8. Journal code: 9100823. ISSN: 0959-4973. Pub. country: England: United Kingdom. Language: English.
AB Topical treatment of skin metastases with a cytotoxic agent is attractive for its easy self-administration and absence of major systemic interference. Miltefosine exerts its cytotoxicity by acting on cell membrane phospholipids and can be administered topically. Twenty breast **cancer** patients with progression of skin metastases were treated with a 6% solution of miltefosine, which was topically administered once daily during the first week and twice daily thereafter. Sixteen out of 20 patients also had metastatic disease at other sites. Concomitant systemic treatment when ongoing for at least 2 months prior to study entry was permitted, and consisted of chemotherapy and hormonal therapy in seven and nine patients, respectively. Prior palliative cytotoxic and hormonal therapy had been administered to 11 and 19 patients, respectively. No grade 3 and 4 toxicity occurred. Miltefosine therapy was discontinued in two patients due to nausea and in one patient due to skin toxicity. Grade 1 and 2 adverse skin reactions, and nausea and vomiting were seen in 11 and two patients, respectively. In 18 patients evaluable for response, four partial responses were noted (response rate 22%), while seven patients had stable disease. Three partial responses were observed in patients in whom the skin lesions were smaller than 1.5 cm2. Median duration of response was 2.5 months and median time to progression for all patients was 1.9 months. In this study topically applied miltefosine for metastatic skin lesions of breast **cancer** showed modest activity in a relatively heavily pretreated patient population, without serious systemic toxicity.

L26 ANSWER 4 OF 47 HCAPLUS COPYRIGHT 2004 ACS on STN
1999:537972 Document No. 131:144715 Process for the preparation of alkylphosphocholines and the production thereof in pure form. **Engel, Jurgen**; Kutscher, Bernd; Schumacher, Wolfgang; Niemeyer, Ulf; Olbrich, Alfred; Nssner, Gerhard (Asta Medica A.-G., Germany). U.S. US 5942639 A 19990824, 5 pp., Cont.-in-part of U. S. Ser. No. 905,817, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1997-938331 19970925. PRIORITY: DE 1991-4122127 19910704; US 1992-905817 19920629.
AB A process for the preparation of C14-C18-alkylphosphocholines by reacting an n-alkanol with a chain length of C14-C18 with phosphorus oxychloride in an inert solvent or also without solvent in the presence or absence of a basic substance in a single vessel process and subsequent reaction of the reaction product in an inert solvent with a choline salt in the presence

of a basic substance to form phosphoric acid diester chloride, subsequent hydrolysis and isolation of alkylphosphocholine as well as optionally purification using a mixed-bed ion exchanger or in successive steps with an acid ion exchanger and a basic ion exchanger. Thus, reaction of POCl3 with hexadecanol in chloroform in the presence of pyridine followed by treatment with choline tosylate, hydrolysis, and Amberlite MB 3 ion exchanger gave 53% hexadecyl phosphocholine. The prepared compds. are useful in treatment for **tumors**.

L26 ANSWER 5 OF 47 MEDLINE on STN DUPLICATE 3

2000093836. PubMed ID: 10628349. Changes of intracellular calcium, fatty acids and phospholipids during miltefosine-induced apoptosis monitored by fluorescence- and 13C NMR-spectroscopy. Henke J; Engelmann J; Kutscher B; Nssner G; **Engel J**; Voegeli R; Leibfritz D. (Institut fur Organische Chemie, Universitat Bremen, Germany.) Anticancer research, (1999 Sep-Oct) 19 (5B) 4027-32. Journal code: 8102988. ISSN: 0250-7005. Pub. country: Greece. Language: English.

AB The alkylphosphocholine Miltefosine (hexadecylphosphocholine, HePC) induces apoptosis in human epithelial KB cells, whereas no such effect can be observed in a resistant clone (KBres). Its mode of action is mediated via the cell membrane, whereas the mechanism is still widely unknown. The use of various spectroscopic methods (fluorescence spectroscopy with Fura-2/AM on viable cells, 13C NMR spectroscopy on lipid extracts) reveals osmotic and metabolic changes in HePC treated sensitive cells. Intracellular free Ca(2+)-concentration increased over 300% of control in apoptotic cells, whereas KBres cells showed only a minor increase and no morphological response typical for apoptosis. The Ca(2+)-influx was mediated via calcium channels in the cell membrane. The HePC-induced influx is prevented by Gd3+, which blocks those calcium channels. Cells, grown in Ca(2+)-free medium, showed no apoptotic behaviour after treatment with HePC. If apoptosis was induced, an increased fatty acid and subsequent phospholipid biosynthesis was observed. This effect seems to be a specific marker of apoptosis in KB cells.

L26 ANSWER 6 OF 47 MEDLINE on STN DUPLICATE 4

1999196387. PubMed ID: 10098751. Phase II trial of topically applied miltefosine solution in patients with skin-metastasized breast **cancer**. Terwogt J M; Mandjes I A; **Sindermann H**; Beijnen J H; ten Bokkel Huinink W W. (Department of Medical Oncology, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Huis, Amsterdam.) British journal of cancer, (1999 Mar) 79 (7-8) 1158-61. Journal code: 0370635. ISSN: 0007-0920. Pub. country: SCOTLAND: United Kingdom. Language: English.

AB Skin deposits from breast **cancer** can present serious therapeutic problems, especially when resistant to conventional therapy. Topical application of a cytotoxic drug may represent an attractive new treatment modality devoid of major systemic toxicity. Miltefosine was selected because of its efficacy in breast **cancer** models. A mixture of alkylated glycerols of various chain lengths and water was used as the pharmaceutical vehicle to dissolve and to further facilitate tissue penetration of miltefosine. In our Institute a phase II study was performed to determine the efficacy and tolerability of topically applied miltefosine in patients with cutaneous metastases from breast **cancer**. Thirty-three patients in total entered the trial. A 6% miltefosine solution was applied once daily in the first week and twice daily in the following weeks. The planned minimum treatment duration was 8 weeks. We found an overall response rate of 43% for 30 evaluable patients, composed of 23% complete response and 20% partial response. The median response duration was 18 weeks, range 8-68. Toxicity consisted mainly of localized skin reactions, which could be controlled by a paraffin-based skin cream and, where appropriate, by dose modification. No systemic toxicities were observed. We conclude that topical

miltefosine is an effective treatment modality in patients with skin metastases from breast **cancer**.

L26 ANSWER 7 OF 47 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
1999250739 EMBASE Inhibitors of signal transduction: The alkylphosphocholines. Hilgard P.; Klenner T.; **Engel J.**. Dr. J. Engel, Research at ASTA Medica AG, Weissmullerstr. 45, D-60001 Frankfurt am Main, Germany. Drug News and Perspectives 12/2 (69-72) 1999. Refs: 38.
ISSN: 0214-0934. CODEN: DNPEED. Pub. Country: Spain. Language: English. Summary Language: English.
AB The experimental **antitumor** activity of the alkylphosphocholines, a new class of signal transduction inhibitors, has been demonstrated repeatedly. The alkylphosphocholines have inhibitory activities on protein kinase C (PKC) and phospholipase C. The PKC pathway of signal transduction may be involved in cellular differentiation and in the induction of apoptosis. Moreover, PKC inhibition by miltefosine may affect **tumor** invasion and metastasis formation. Miltefosine may also interfere with immunological mechanisms. Finally, in addition to its **antitumor** activity, miltefosine also exerts substantial effects on a number of Leishmania strains. In brief, miltefosine and other alkylphosphocholines interact with signal transduction components of cellular functions such as differentiation, growth control, migration, **tumor** promotion and cell death. Due to these activities, this new class of pharmacophores has a great potential in the treatment of **cancer** and certain parasitic diseases.

L26 ANSWER 8 OF 47 HCAPLUS COPYRIGHT 2004 ACS on STN
1998:388769 Document No. 129:49640 Use of dopamine receptor antagonists in palliative **tumor** therapy. Nickel, Bernd; Klenner, Thomas; Hilgard, Peter; **Engel, Juergen** (Asta Medica A.-G., Germany). Ger. Offen. DE 19650778 A1 19980610, 18 pp. (German). CODEN: GWXXBX. APPLICATION: DE 1996-19650778 19961206.
AB The loss in body weight which occurs as a side effect in **tumor** therapy with alkylphosphocholines such as miltefosine can be prevented by appetite-stimulating dopamine receptor antagonists such as domperidone and pimozide without interfering with the **antitumor** activity of the alkylphosphocholine and without causing addnl. side effects, as shown in expts. on **tumor**-bearing rats.

L26 ANSWER 9 OF 47 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5
1999:108853 Document No. 130:320481 Apoptotic effects of hexadecylphosphocholine on resistant and nonresistant cells monitored by NMR spectroscopy. Henke, J.; Engelmann, J.; Flogel, U.; Pfeuffer, J.; Kutscher, B.; Nossner, G.; **Engel, J.**; Voegeli, R.; Leibfritz, D. (Institut fur Organische Chemie, Universitat Bremen, Bremen, D-28334, Germany). Drugs of Today, 34(Suppl. F), 37-50 (English) 1998. CODEN: MDACAP. ISSN: 0025-7656. Publisher: Prous Science.
AB The alkylphosphocholine miltefosine (hexadecylphosphocholine, HPC) has anti-neoplastic potential in vivo and in vitro. Its mode of action is mediated via the cell membrane, but the mechanism is still unclear. In this study it was found that the use of various NMR spectroscopic methods (diffusion-weighted 1H- and 31P-NMR spectroscopy on viable cells, multinuclear NMR spectroscopy on lipid exts.) revealed metabolic and morphol. changes in HPC-treated **tumor** cells. Miltefosine ($\leq$100 μM) was able to induce apoptosis in human epithelial KB cells, whereas in a resistant subline of this cell line (KBres) no such effect was observed In both cell lines, necrosis took place if they have been treated with high concns. of HPC ($\geq$200 μM). Apoptotic cells decreased in cell volume, whereas cells swelled under necrotic conditions. An early effect of HPC treatment in KB and KBres was an

increase of the neutral lipids triacylglycerol and diacylglycerol associated with changes of the intracellular signal transduction by the latter. If apoptosis was induced, an increased fatty acid biosynthesis was observed This effect seems to be a specific marker of apoptosis in KB cells.

L26 ANSWER 10 OF 47 MEDLINE on STN
97344885. PubMed ID: 9201252. The development of alkylphosphocholines as signal transduction inhibitors: experimental and clinical challenges. Hilgard P; Pohl J; **Engel** J. Journal of cancer research and clinical oncology, (1997) 123 (5) 286-7. Journal code: 7902060. ISSN: 0171-5216. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB Alkylphosphocholines are a new class of anticancer agents. Their mode of action is considered to be related to the inhibition of phospholipase C and protein kinase C. These enzymes play a major role in intracellular signalling pathways. Their inhibition by alkylphosphocholines leads in the dimethylbenzanthracene-induced mammary **carcinoma** of the rat to a response pattern similar to that of the antiestrogen zindoxifene. This suggests that the inhibition of transcription factor formation might be the common pathway for alkylphosphocholines and antihormones. Based on the experimental dose-response pattern, new clinical strategies for dose finding and response evaluation will have to be developed for inhibitors of signal transduction, such as alkylphosphocholines.

L26 ANSWER 11 OF 47 MEDLINE on STN DUPLICATE 6
97300509. PubMed ID: 9155530. D-21266, a new heterocyclic alkylphospholipid with **antitumour** activity. Hilgard P; Klenner T; Stekar J; Nossner G; Kutscher B; **Engel J.** (Corporate Research ASTA Medica AG, Frankfurt am Main, Germany.) European journal of cancer (Oxford, England : 1990), (1997 Mar) 33 (3) 442-6. Journal code: 9005373. ISSN: 0959-8049. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The aim of this study was to determine the **antitumour** effects of D-21266 in a rodent **tumour** model. Hexadecylphosphocholine (INN: Miltefosine) represents the first anticancer agent which was specifically formulated for topical use in **cancer** patients. The development as an oral drug was hampered by the gastrointestinal toxicity. Hexadecylphosphocholine derivatives were sought with a better therapeutic index. Octadecyl-(1,1-dimethyl-4-piperidylio) phosphate (D-21266) was identified as a suitable candidate. This compound is highly active in vitro inhibiting the growth of a number of human **cancer** cell lines. Mammary **carcinomas** were induced in Sprague-Dawley rats using DMBA, and oral doses of D-21266, in various schedules, were given to the animals. A high antineoplastic potency was observed without inducing loss of body weight at highly effective doses. The **antitumour** effect could be enhanced by introducing a dose schedule consisting of a high loading dose followed by a low maintenance dose, both of which are only marginally active when given alone. Therefore, D-21266 with its favourable pharmacological and toxicological profile, warrants evaluation in the clinic. However, the concept of clinical trials requires new approaches to dose finding and response evaluation, because the dose-response relationship of this compound is distinctly different from that of classical cytostatic agents.

L26 ANSWER 12 OF 47 HCAPLUS COPYRIGHT 2004 ACS on STN
1997:628445 Document No. 127:239179 Validation of an HPTLC method for impurities testing and determination of the log P value of a new phospholipid. Rischer, Matthias; Schnell, Horst; Greguletz, Roland; Wolf-Heuss, Elisabeth; **Engel, Jurgen** (Asta Medica AG, Frankfurt am Main, D-60001, Germany). Journal of Planar Chromatography--Modern TLC, 10(4), 290-297 (English) 1997. CODEN: JPCTE5. ISSN: 0933-4173. Publisher: Research Institute for Medicinal Plants.
AB A TLC method was developed for the detection of a new, non-UV-active

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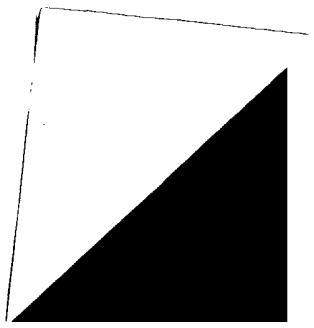
phospholipid **cancer**-treatment drug, D-21266. Validation of the method was performed according to ICH and CPMP requirements for validation, detection, and quantification of impurities in new drug substances. In addition the log P value was determined by use of simple partition method then TLC anal. The log P value for phospholipids containing more than one polar head group was shown to be dependent on pH.

L26 ANSWER 13 OF 47 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
97133817 EMBASE Document No.: 1997133817. Heterocyclic alkylphospholipids with an improved therapeutic range. Hilgard P.; Stekar J.; Klenner T.; Nossner G.; Kutscher B.; **Engel J.**. P. Hilgard, Experimental Cancer Research Dept., ASTA Medica AG, Weismullerstr. 45, D-60314 Frankfurt am Main, Germany. Advances in Experimental Medicine and Biology 416/- (157-164) 1997.
Refs: 6.
ISSN: 0065-2598. CODEN: AEMBAP. Pub. Country: United States. Language: English.

L26 ANSWER 14 OF 47 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 7
1996:471069 Document No. 125:157936 Early stage monitoring of miltefosine-induced apoptosis in KB cells by multinuclear NMR spectroscopy. Engelmann, Joern; Henke, Joachim; Willker, Wieland; Kutscher, Bernhard; Noessner, Gerhard; **Engel, Juergen;** Leibfritz, Dieter (Institut fur Organische Chemie, Universitat Bremen, Bremen, 28334, Germany). Anticancer Research, 16(3B, Proceedings of the Special Symposium on "Lipid Metabolism and Function in Cancer", 1995), 1429-1439 (English) 1996. CODEN: ANTRD4. ISSN: 0250-7005. Publisher: Anticancer Research.
AB Synthetic ether lipids, like miltefosine (hexadecylphosphocholine), an alkylphosphocholine, are antineoplastic agents in vitro and in vivo. Their mode of action is mediated via the cell membrane, but the mechanism is still unclear. Miltefosine induces apoptosis in human epithelial KB cells, but slows down only proliferation in rat C6 glioma cells. NMR spectroscopy on lipid exts. reveals increased diacylglycerol and triacylglycerol biosynthesis in KB cells prior to DNA fragmentation indicating a CTP:phosphocholine-cytidylyltransferase (CT) inhibition by the drug. Although C6 cells were morphol. affected by alterations in phospholipid composition and metabolism by a long term treatment (23 days) with the drug, no persistent diacylglycerol increase is observed

L26 ANSWER 15 OF 47 MEDLINE on STN DUPLICATE 8
97277766. PubMed ID: 9131142. Heterocyclic alkylphospholipids with an improved therapeutic range. Hilgard P; Stekar J; Klenner T; Nossner B; Kutscher B; **Engel J.** (ASTA Medica AG, Experimental Cancer Research Department, Frankfurt am Main, Germany.) Advances in experimental medicine and biology, (1996) 416 157-64. Ref: 6. Journal code: 0121103. ISSN: 0065-2598. Pub. country: United States. Language: English.

L26 ANSWER 16 OF 47 HCAPLUS COPYRIGHT 2004 ACS on STN
1995:371399 Document No. 122:265838 Synthesis, **antitumor** activity, and tolerability of phospholipids containing nitrogen homologs. Stekar, Jurij; Noessner, Gerhard; Kutscher, Bernhard; **Engel, Juergen;** Hilgard, Peter (Weismuellerstrasse, Frankfurt, D-60314, Germany). Angewandte Chemie, International Edition in English, 34(2), 238-40 (English) 1995. CODEN: ACIEAY. ISSN: 0570-0833. Publisher: VCH.
GI



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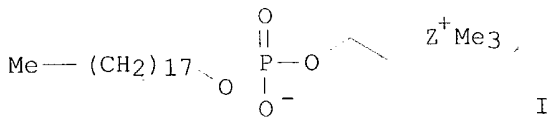
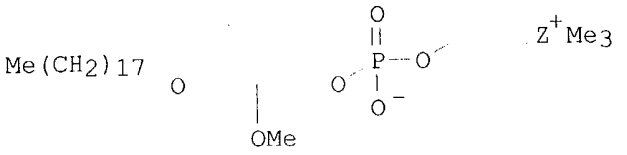


I

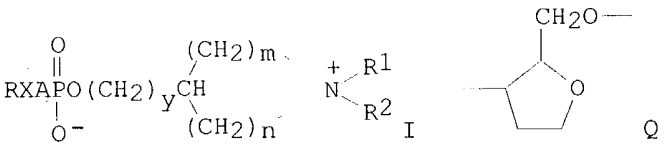


II

AB Glycerophospholipids homologs I and II (Z = P, As) were prepared and tested for their **antitumor** activities. Cytotoxicity of I (Z = N, P, As) on cell lines L1210, KB, and DS is reported.

L26 ANSWER 17 OF 47 HCAPLUS COPYRIGHT 2004 ACS on STN
1994:564005 Document No. 121:164005 Stabilized solutions of hexadecylphosphocholine in glycerol alkyl ether. **Engel, Juergen**; Wolf-Heuss, Elisabeth; Orth, Helmut; Wichert, Burkhard; Sauerbier, Diester (ASTA Medica Aktiengesellschaft, Germany). Eur. Pat. Appl. EP 593897 A1 19940427, 8 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE. (German). CODEN: EPXXDW. APPLICATION: EP 1993-114672 19930913. PRIORITY: DE 1992-4235911 19921023.
AB Solns. containing alkyl phosphocholines and glycerol alkyl ethers with **antitumor** activity are stabilized by buffering to pH 4-6, e.g. with citric acid and NaOH, to prevent peroxide formation and a drop in pH.

L26 ANSWER 18 OF 47 HCAPLUS COPYRIGHT 2004 ACS on STN
1994:605667 Document No. 121:205667 Preparation of new phospholipid derivatives (phosphates containing heterocycle moieties) as drugs. Noessner, Gerhard; Kutscher, Bernhard; **Engel, Juergen**; Schumacher, Wolfgang; Stekar, Jurij; Hilgard, Peter (Aste Medica AG, Germany). Ger. Offen. DE 4222910 A1 19940113, 14 pp. (German). CODEN: GWXXBX. APPLICATION: DE 1992-4222910 19920711.
GI



I Q

US equiv.

AB Title compds. I [R = C10-24 alkyl; R1, R2 = H, (un)substituted alkyl; A = single bond, -(CH2)3O-, -CH2-CH2-O-, -CH2-CHMe-O-, -S-(CH2)8-O-, Q; y = 0, 1-3 integer; m, n = 0 or an integer with the proviso that m+n = 2-8; X = O, S, NH], useful as inhibitors of **tumors**, leishmaniasis, skin diseases, etc., (no data),are prepared E.g., 4-hydroxy-1,1-dimethylpiperidinium tosylate was added to a mixture of phosphorus oxychloride and 1-octadecanol in CHCl3 at 5-10°, DMF and pyridine were added, and the resulting mixture was stirred at room temperature for 24 h to give 10% I [R = octadecyl, R1 = R2 = Me, X = O, m = n = 2, yr = 0, A = single bond].

L26 ANSWER 19 OF 47 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 9

Searched by: Mary Hale 571-272-2507 REM 1D86

95031791 EMBASE Document No.: 1995031791. Overview of the clinical development of miltefosine solution (Miltex®) for the treatment of cutaneous breast **cancer**. Burk K.; David M.; Junge K.; **Sindermann H.**. ASTA Medica AG,D-60314 Frankfurt, Germany. Drugs of Today 30/SUPPL. B (59-72) 1994.
ISSN: 0025-7656. CODEN: MDACAP. Pub. Country: Spain. Language: German. Summary Language: German; English.

AB The safety of topically administered Miltex® (6% miltefosine solution) was assessed by evaluation of pooled data from 443 patients with cutaneous breast **cancer**. Local skin reactions accompanied by paraesthesia were common adverse reactions. Changes in laboratory parameters were infrequent (2.4%). The integrated analysis of phase II data from 302 evaluable patients revealed a substantial number of objective remissions of cutaneous breast **cancer** manifestations. A response rate of 41% was seen in patients with multiple small nodules or purely superficial infiltrations. Against this background Miltex® can be regarded as a valuable addition to the range of palliative therapies for breast **cancer**. Topical miltefosine can still be used when surgical, radiological and systemic hormone or chemotherapy have been exhausted. It can also be safely and effectively combined with systemic **cancer** treatment.

L26 ANSWER 20 OF 47 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 10

94110473 EMBASE Document No.: 1994110473. Miltefosine solution: Prognostic factors for the outcome of topical treatment of skin metastatic breast **cancer**. **Sindermann H.**; Junge K.; Burk K.. Abteilung Klinische Tumorforschung, ASTA Medica AG, Weismullerstrasse 45,D-60314 Frankfurt, Germany. Onkologie 17/1 (21-26) 1994.
ISSN: 0378-584X. CODEN: ONKOD2. Pub. Country: Germany. Language: English. Summary Language: English; German.

AB Background. Miltefosine solution has been used for the topical treatment of skin metastases from breast **cancer**. An overview analysis of data from clinical phase II trials has been performed to identify prognostic factors for efficacy and tolerability. Materials and Methods. Results from 287 patients treated with miltefosine solution in phase II trials have been included in an overview analysis. This involved an extramural review of data on efficacy. Prognostic factors for quality of response and time to progression were analyzed by a logit and a Weibull model, respectively. Results: Depth of infiltration was identified as the most relevant prognostic factor for response of skin lesions. A 39% response rate (complete, partial and minor responses) was achieved in patients having small nodular lesions (diameter of nodules up to 1 cm) and/or lymphangitic infiltration without deep subcutaneous **tumor** mass. In patients with lesions outside these limits, the rate of objective regressions was 13% . In case miltefosine solution was added on top of a systemic endocrine therapy which had failed to control the skin lesions, a response rate of 38% to the combination was observed (median time to progression of skin lesions 27 weeks). Pruritus was the most frequently reported local skin reaction (31%), followed by erythema (18%), and pain and burning (10% each). In virtual absence of systemic side effects, local reactions were generally tolerable. A decrease in the hazard rate for local reactions with increasing duration of treatment indicates that there is no significant risk for a sensitization. Conclusions: Miltefosine solution is an effective and tolerable new treatment modality, especially in patients with cutaneous lesions with limited depth of infiltration. Prognostic factors identified by this analysis may serve as an aid in treatment planning for individual patients, but also as a data base for future, confirmatory trials.

L26 ANSWER 21 OF 47 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

Searched by: Mary Hale 571-272-2507 REM 1D86

95031782 EMBASE Document No.: 1995031782. Clinical aspects of miltefosine and its topical formulation Miltex®: Introduction. Hilgard P.; **Engel J.**. ASTA Medica AG, Weismuller Str. 45,D-60134 Frankfurt am Main, Germany. Drugs of Today 30/SUPPL. B (3-4) 1994. ISSN: 0025-7656. CODEN: MDACAP. Pub. Country: Spain. Language: English.

L26 ANSWER 22 OF 47 MEDLINE on STN DUPLICATE 11

94064954. PubMed ID: 8245262. Topical administration of hexadecylphosphocholine in patients with cutaneous lymphomas: results of a phase I/II study. Dummer R; Krasovec M; Roger J; **Sindermann H;** Burg G. (Department of Dermatology, University of Zurich Medical School, Switzerland.) Journal of the American Academy of Dermatology, (1993 Dec) 29 (6) 963-70. Journal code: 7907132. ISSN: 0190-9622. Pub. country: United States. Language: English.

AB BACKGROUND: Hexadecylphosphocholine is a new antineoplastic drug that inhibits **tumor** cell growth directly and, in addition, might have immunoregulatory properties. OBJECTIVES: We investigated the topical application of this phospholipid in patients with cutaneous lymphoma. METHODS: Twenty-four patients with histologically documented cutaneous lymphoma were treated for 8 weeks. Lesions that responded to treatment were biopsied and evaluated histologically. RESULTS: Of 15 patients with cutaneous T-cell lymphomas, 12 were evaluable. Two complete remissions, four partial remissions, and one minor remission were observed. Of seven patients with B-cell lymphomas, six were evaluable. One complete remission, three partial remissions, one case of stable disease, and one case of progressive disease were seen. However, histologic monitoring demonstrated only a partial clearing of infiltrating lymphocytes in lesions that showed a partial or complete response clinically. Both patients with lymphomatoid papulosis had complete clearing of the lesions clinically. An objective response rate (partial and complete response) of 56% (10/18) was achieved in the patients with cutaneous lymphoma who were treated in this study. CONCLUSION: Hexadecylphosphocholine appears to be effective topically in the treatment of some cases of cutaneous lymphomas.

L26 ANSWER 23 OF 47 MEDLINE on STN DUPLICATE 12

94080724. PubMed ID: 8258191. Antineoplastic activity and tolerability of a novel heterocyclic alkylphospholipid, D-20133. Stekar J; Hilgard P; Voegeli R; Maurer H R; **Engel J;** Kutscher B; Nossner G; Schumacher W. (Department of Experimental Cancer Research, ASTA Medica AG, Frankfurt/Main, Germany.) Cancer chemotherapy and pharmacology, (1993) 32 (6) 437-44. Journal code: 7806519. ISSN: 0344-5704. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Octadecyl-[2-(N-methylpiperidinio)ethyl]-phosphate (OMPEP, D-20133), a heterocyclic analogue of hexadecylphosphocholine (MIL), has been synthesized in an attempt to increase the therapeutic range of the parent compound. The antineoplastic activity of the novel alkylphospholipid was compared with that of MIL in dimethylbenz(a)anthracene-induced mammary **carcinoma** of the rat. Using **tumors** of different sizes and repeated daily doses as well as high single doses, we achieved marked remissions with either compound. However, the therapeutic range of OMPEP was broader than that of the parent drug. Furthermore, the emetic potential of OMPEP tested on ferrets was distinctly less pronounced than that of MIL. In vitro the new alkylphospholipid proved to be more active than MIL in all cell lines tested, and its differentiation-inducing capacity turned out to be superior to that of MIL. No hematological toxicity was observed at various OMPEP doses during a 3-week treatment period.

L26 ANSWER 24 OF 47 MEDLINE on STN DUPLICATE 13

93115198. PubMed ID: 8418086. **Antitumour** activity of miltefosine alone and after combination with platinum complexes on MXT mouse mammary **carcinoma** models. Spruss T; Bernhardt G; Schonenberger H;

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Engel J. (Universitat Regensburg, Institut fur Pharmazie, Federal Republic of Germany.) Journal of cancer research and clinical oncology, (1993) 119 (3) 142-9. Journal code: 7902060. ISSN: 0171-5216. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Miltefosine, an alkylphosphocholine structurally related to alkyllysophospholipids showed highly selective **antitumour** activity against the hormone-sensitive variant of the s.c. transplantable MXT mouse mammary adenocarcinoma, the ovary-dependent MXT (M3.2), whereas it was inactive against the hormone-insensitive MXT (M3.2) OVEX variant. A dose of 32 mg/kg miltefosine p.o. daily for 5 weeks was well tolerated. Histopathological evaluation gave no signs of gastroenteral toxicity. After therapy the microarchitecture of the MXT (M3.2) **tumours** changed from that of a moderately differentiated adenocarcinoma to that of an anaplastic mammary **carcinoma**. A dose of 16 mg/kg miltefosine p.o. daily, though in effective per se, enhanced the **antitumour** activity of suboptimal i.p. doses of cisplatin and the hormone-like platinum analogue meso-1,2-bis(2,6-dichloro-4-hydroxyphenyl) ethylenediamine]dichloroplatinum(II). Furthermore, it was shown, that miltefosine exhibited no (anti)hormonal properties. However, the mechanism of action of miltefosine remains unclear.

L26 ANSWER 25 OF 47 EMBASE on STN

93139045 EMBASE Document No.: 1993139045. Phase II trial of orally administered miltefosine in advanced colorectal **cancer**. Becher R.; Kloke O.; Fuger A.; Bremer K.; Drozd A.; Kleeberg U.R.; Fritze D.; Rieche K.; **Sindermann H.**. Innere Klinik und Poliklinik, Westdeutsches Tumorzentrum, Universitatsklinikum, Hufelandstrasse 55,D-4300 Essen 1, Germany. Onkologie 16/1 (11-15) 1993. ISSN: 0378-584X. CODEN: ONKOD2. Pub. Country: Germany. Language: English. Summary Language: English; German.

AB Background: Treatment results in advanced colorectal **cancer** (CC) remain unsatisfactory and palliative, with 5-fluorouracil with or without calcium folinate being the only drug able to induce clinically acceptable response rates. Patients and Methods: A clinical phase II study is presented with an oral formulation of the phospholipid derivative miltefosine (MIL) in patients with advanced colorectal **cancer**. Patients were stratified according to pretreatment. Only non-pretreated or pretreated patients who had received 5-fluorouracil with or without calcium folinate were accepted. MIL was given as capsule twice daily at a single dose of 50 mg for the 1st week with dose escalation to 150 mg (50 mg x 3) in the 2nd week and subsequently in case of good tolerability. Nine weeks were considered the minimalduration of treatment. Results: 54 patients were evaluable for toxicity and 44 were evaluable for response. A short-lived partial response was observed in one pretreated female patient with multiple lung lesions, a 'no change' status in 14 patients, including 8 nonpretreated patients (42%) and 6 pretreated patients (24%). Side effects were distinct, with loss of appetite, nausea and vomiting up to grade 4 WHO and weight loss of more than 5 kg in 3 months in a considerable number of patients. Furthermore, an increase of leukocyte and platelet counts was observed during the first 2 months of treatment. Conclusion: Oral MIL is considerably toxic and has only marginal therapeutic activity in patients with colorectal **cancer**.

L26 ANSWER 26 OF 47 BIOSIS on STN

1993:300830 Document No.: PREV199396019055. Phase II trial of orally administered miltefosine in advanced colorectal **cancer**. Becher, Reinhard [Reprint author]; Kloke, O.; Fueger, A.; Bremer, K.; Drozd, A.; Kleeberg, U. R.; Fritze, D.; Rieche, K.; **Sindermann, H.**. Innere Klin. Poliklin. Tumorforschung, Westdeutsches Tumorzentrum Essen, Universitaetsklin. Essen, Hufelandstrasse 55, D-W-4300 Essen, Germany.

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Onkologie, (1993) Vol. 16, No. 1, pp. 1-15.
CODEN: ONKOD2. ISSN: 0378-584X. Language: English.

AB Background: Treatment results in advanced colorectal **cancer** (CC) remain unsatisfactory and palliative, with 5-fluorouracil with or without calcium folinate being the only drug able to induce clinically acceptable response rates. Patients and Methods: A clinical phase II study is presented with an oral formulation of the phospholipid derivative miltefosine (MIL) in patients with advanced colorectal **cancer**. Patients were stratified according to pretreatment. Only non-pretreated or pretreated patients who had received 5-fluorouracil with or without calcium folinate were accepted. MIL was given as capsule twice daily at a single dose of 50 mg for the 1st week with dose escalation to 150 mg (50 mg times 3) in the 2nd week and subsequently in case of good tolerability. Nine weeks were considered the minimal duration of treatment. Results: 54 patients were evaluable for toxicity and 44 were evaluable for response. A short-lived partial response was observed in one pretreated female patient with multiple lung lesions, a 'no change' status in 14 patients, including 8 nonpretreated patients (42%) and 6 pretreated patients (24%). Side effects were distinct, with loss of appetite, nausea and vomiting up to grade 4 WHO and weight loss of more than 5 kg in 3 months in a considerable number of patients. Furthermore, an increase of leukocytes and platelet counts was observed during the first 2 months of treatments. Conclusion: Oral MIL is considerably toxic and has only marginal therapeutic activity in patients with colorectal **cancer**.

L26 ANSWER 27 OF 47 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1992:533450 Document No.: PREV199243119150; BR43:119150. HEXADECYLPHOSPHOCHOLINE IN THE TOPICAL TREATMENT OF SKIN METASTASES IN BREAST **CANCER** PATIENTS. UNGER C [Reprint author]; **SINDERMANN H**; PEUKERT M; HILGARD P; **ENGEL J**; EIBL H. DIV HEMATOL/ONCOL, DEP OF INTERNAL MED, UNIV HOSP, GOETTINGEN, D-W-3400 GOETTINGEN, GERMANY. Prog. Exp. Tumor Res., (1992) pp. 153-159. EIBL, H., P. HILGARD AND C. UNGER (ED.). PROGRESS IN EXPERIMENTAL TUMOR RESEARCH, VOL. 34. ALKYLPHOSPHOCHOLINES: NEW DRUGS IN CANCER THERAPY. X+173P. S. KARGER AG: BASEL, SWITZERLAND; NEW YORK, NEW YORK, USA. ILLUS. Publisher: Series: Progress in Experimental Tumor Research.
CODEN: PEXTAR. ISSN: 0079-6263. ISBN: 3-8055-5464-8. Language: ENGLISH.

L26 ANSWER 28 OF 47 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1992:533437 Document No.: PREV199243119137; BR43:119137. SYNTHESIS OF HEXADECYLPHOSPHOCHOLINE MILTEFOSINE. EIBL H [Reprint author]; **ENGEL J**. MAX-PLANCK-INSTITUT FUER BIOPHYSIKALISCHE CHEMIE, POSTFACH 2841, D-W-3400 GOETTINGEN, GERMANY. Prog. Exp. Tumor Res., (1992) pp. 1-5. EIBL, H., P. HILGARD AND C. UNGER (ED.). PROGRESS IN EXPERIMENTAL TUMOR RESEARCH, VOL. 34. ALKYLPHOSPHOCHOLINES: NEW DRUGS IN CANCER THERAPY. X+173P. S. KARGER AG: BASEL, SWITZERLAND; NEW YORK, NEW YORK, USA. ILLUS. Publisher: Series: Progress in Experimental Tumor Research.
CODEN: PEXTAR. ISSN: 0079-6263. ISBN: 3-8055-5464-8. Language: ENGLISH.

L26 ANSWER 29 OF 47 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1992:384574 Document No.: PREV199243051524; BR43:51524. MILTEFOSINE SOLUTION IN THE TOPICAL TREATMENT OF SKIN METASTASES IN BREAST **CANCER** PATIENTS. UNGER C [Reprint author]; **SINDERMANN H**; HILGARD P; **ENGEL J**; QUEISSER W; EIBL H. MED UNIV CLIN, D-3400 GOETTINGEN, GER. Proceedings of the American Association for Cancer Research Annual Meeting, (1992) Vol. 33, pp. 214.
Meeting Info.: 83RD ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, SAN DIEGO, CALIFORNIA, USA, MAY 20-23, 1992. PROC AM ASSOC CANCER RES ANNU MEET.

Searched by: Mary Hale 571-272-2507 REM 1D86

ISSN: 0197-016X. Language: ENGLISH.

L26 ANSWER 30 OF 47 MEDLINE on STN
93067021. PubMed ID: 1438799. Topical application of hexadecylphosphocholine in patients with cutaneous lymphomas. Dummer R; Roger J; Vogt T; Becker J; Hefner H; **Sindermann H**; Burg G. (Department of Dermatology, University of Wurzburg Medical School, FRG.) Progress in experimental tumor research. Fortschritte der experimentellen Tumorforschung. Progres de la recherche experimentale des tumeurs, (1992) 34 160-9. Journal code: 0376446. ISSN: 0079-6263. Pub. country: Switzerland. Language: English.

L26 ANSWER 31 OF 47 MEDLINE on STN
93067020. PubMed ID: 1438798. Hexadecylphosphocholine in the topical treatment of skin metastases in breast **cancer** patients. Unger C; **Sindermann H**; Peukert M; Hilgard P; **Engel J**; Eibl H. (Department of Internal Medicine, University Hospital Gottingen, FRG.) Progress in experimental tumor research. Fortschritte der experimentellen Tumorforschung. Progres de la recherche experimentale des tumeurs, (1992) 34 153-9. Journal code: 0376446. ISSN: 0079-6263. Pub. country: Switzerland. Language: English.

L26 ANSWER 32 OF 47 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 14
92002003 EMBASE Document No.: 1992002003. Phase I study of weekly oral miltefosine (hexadecyl-phosphocholine) in **cancer** patients. Danhauser-Riedl S.; Drozd A.; Zafferani M.; Bruntsch U.; Peukert M.; **Sindermann H.**; Prauer H.W.; Siewert J.R.; Rastetter J.; Berdel W.E.. Department of Hematology and Oncology, Klinikum Steglitz, Freie Universitat Berlin, 30 Hindenburgdamm, 1000 Berlin 45, Germany. Onkologie 14/5 (392-400) 1991.
ISSN: 0378-584X. CODEN: ONKOD2. Pub. Country: Germany. Language: English. Summary Language: English; German.

L26 ANSWER 33 OF 47 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
1991:422206 Document No.: PREV199141071751; BR41:71751. HEXADECYLPHOSPHOCHOLINE D-18506 A NEW PHOSPHOLIPID WITH HIGHLY SELECTIVE **ANTITUMOR** ACTIVITY. SCHUMACHER W [Reprint author]; STEKAR J; HILGARD P; **ENGEL J**; EIBL H; UNGER C. ASTA PHARMA AG, D-6000 FRANKFURT 1, W GER. (1990) pp. 287-290. HANIN, I. AND G. PEPEU (ED.). PHOSPHOLIPIDS: BIOCHEMICAL, PHARMACEUTICAL, AND ANALYTICAL CONSIDERATIONS; 5TH INTERNATIONAL COLLOQUIUM ON LECITHIN, CANNES, FRANCE, APRIL 10-12, 1989. IX+318P. PLENUM PRESS: NEW YORK, NEW YORK, USA; LONDON, ENGLAND, UK. ILLUS.
ISBN: 0-306-43698-1. Language: ENGLISH.

L26 ANSWER 34 OF 47 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
1991:194040 Document No.: PREV199140091320; BR40:91320. PHASE I STUDY WITH DAILY HEXADECYLPHOSPHOCHOLINE IN PATIENTS WITH **MALIGNANT** DISEASE. UNGER C [Reprint author]; EIBL H; VON HEYDEN H W; PEUKERT M; **SINDERMANN H**; NAGEL G A. UNIV HOSP, D-3400 GOETTINGEN. Journal of Cancer Research and Clinical Oncology, (1990) Vol. 116, No. SUPPL. PART 2, pp. 993.
Meeting Info.: 15TH INTERNATIONAL CANCER CONGRESS, HAMBURG, GERMANY, AUGUST 16-22, 1990. J CANCER RES CLIN ONCOL.
CODEN: JCROD7. ISSN: 0171-5216. Language: ENGLISH.

L26 ANSWER 35 OF 47 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
90341788 EMBASE Document No.: 1990341788. Hexadecylphosphocholine (D-18506),

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a new phospholipid with highly selective **antitumor** activity.
Engel J.; Schumacher W.; Hilgard P.; Stekar J.; Eibl H.; Unger C..
ASTA Pharma AG, Postfach 10 01 05, D-6000 Frankfurt 1, Germany. Archiv der Pharmazie 323/8 (547) 1990.
ISSN: 0365-6233. CODEN: ARPMAS. Pub. Country: Germany. Language: English.

L26 ANSWER 36 OF 47 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
1991:172175 Document No.: PREV199140080635; BR40:80635. AN IN-VITRO SCREENING SYSTEM FOR PHOSPHOLIPIDS WITH **ANTITUMOR** ACTIVITY. VOEGELI R [Reprint author]; ECHARTI C; HILGARD P; STEKAR J; MAURER H R; UNGER C; SCHUMACHER W; NOSSNER G; KUTSCHER B; **ENGEL J.** ASTA PHARMA AG, D-4800 BIELEFELD 14. Journal of Cancer Research and Clinical Oncology, (1990) Vol. 116, No. SUPPL. PART 1, pp. 452.
Meeting Info.: 15TH INTERNATIONAL CANCER CONGRESS, HAMBURG, GERMANY, AUGUST 16-22, 1990. J CANCER RES CLIN ONCOL.
CODEN: JCROD7. ISSN: 0171-5216. Language: ENGLISH.

L26 ANSWER 37 OF 47 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
1991:195937 Document No.: PREV199140093217; BR40:93217. CANCEROSTATIC ALKYL PHOSPHOCHOLINES. **ENGEL J** [Reprint author]; EIBL H; UNGER C; HILGARD P; SCHUMACHER W. FRANKFURT, FRG. Fett Wissenschaft Technologie, (1990) Vol. 92, No. 11, pp. 435.
Meeting Info.: 46TH ANNUAL MEETING OF THE GERMAN SOCIETY FOR FAT SCIENCE, NUERNBERG, GERMANY, SEPTEMBER 24-27, 1990. FETT WISS TECHNOL.
Language: GERMAN.

L26 ANSWER 38 OF 47 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
1991:195939 Document No.: PREV199140093219; BR40:93219. ALKYL PHOSPHOCHOLINE PRECLINICAL STUDIES AND FIRST CLINICAL RESULTS WITH A NEW SUBSTANCE CLASS WITH SELECTIVITY ANTI-**TUMOR** PROPERTIES. UNGER C [Reprint author]; **ENGEL J**; EIBL H. GOETTINGEN, FRG. Fett Wissenschaft Technologie, (1990) Vol. 92, No. 11, pp. 435.
Meeting Info.: 46TH ANNUAL MEETING OF THE GERMAN SOCIETY FOR FAT SCIENCE, NUERNBERG, GERMANY, SEPTEMBER 24-27, 1990. FETT WISS TECHNOL.
Language: GERMAN.

L26 ANSWER 39 OF 47 HCAPLUS COPYRIGHT 2004 ACS on STN
1991:505604 Document No. 115:105604 Hexadecylphosphocholine (D-18506): a new phospholipid with highly selective **antitumor** activity.
Schumacher, W.; Stekar, J.; Hilgard, P.; **Engel**, J.; Eibl, H.; Unger, C. (ASTA Pharma A.-G., Frankfurt, D-6000/1, Germany).
Phospholipids: Biochem., Pharm., Anal. Consid., [Proc. Int. Colloq. Lecithin], 5th, Meeting Date 1989, 287-90. Editor(s): Hanin, Israel; Pepeu, Giancarlo. Plenum: New York, N. Y. (English) 1990. CODEN: 57HFAS.
AB A symposium report with 4 refs.

L26 ANSWER 40 OF 47 MEDLINE on STN DUPLICATE 15
91105773. PubMed ID: 2272039. Hexadecylphosphocholine in the topical treatment of skin metastases in breast **cancer** patients. Unger C; Peukert M; **Sindermann H**; Hilgard P; Nagel G; Eibl H. (Department of Internal Medicine, University Hospital, Gottingen, Federal Republic of Germany.) Cancer treatment reviews, (1990 Sep) 17 (2-3) 243-6. Journal code: 7502030. ISSN: 0305-7372. Pub. country: ENGLAND: United Kingdom.
Language: English.
AB Widespread local recurrence of breast **cancer**, untreatable by surgery or radiation therapy, can present a serious therapeutic problem predominantly in patients refractory to systemic therapy. In a phase I trial hexadecylphosphocholine, a new agent with high membrane affinity and antineoplastic activity was applied topically to affected skin areas of

breast **cancer** patients. The results provide evidence that hexadecylphosphocholine may be an active agent in the topical treatment of skin metastases.

L26 ANSWER 41 OF 47 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 16
90142420 EMBASE Document No.: 1990142420. [Hexadecylphosphocholine, a new etherlipid analogue]. HEXADECILFOSFOCOLINA, UN NUEVO ANALOGO ETERLIPIDICO. ESTUDIOS IN VITRO E IN VIVO SOBRE SU ACTIVIDAD ANTINEOPLASTICA. Unger C.; Damenz W.; Fleer E.A.M.; Kim D.J.; Breiser A.; Hilg ard P.; **Engel J.**; Nagel G.; Eibi H.. Department of Internal Medicine, Division of Hematology/Oncology, University of Gottingen, Robert-Koch-Strasse 40, D-3400 Gottingen, Germany. Oncologia 13/2 (64-69) 1990. ISSN: 0378-4835. CODEN: ONCIED. Pub. Country: Spain. Language: Spanish. Summary Language: English.

L26 ANSWER 42 OF 47 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
1990:125575 Document No.: PREV199038059785; BR38:59785. HEXADECYLPHOSPHOCHOLINE AN ALKYLPHOSPHOCHOLINE WITH MAJOR PRECLINICAL **ANTITUMOR** ACTIVITY. HILGARD P [Reprint author]; STEKAR J; HARLEMAN J H; **ENGEL J**; UNGER C; EIBL H; NAGEL G. ASTA PHARMA AG, D-4800 BIELEFELD 14, FRG. Investigational New Drugs, (1989) Vol. 7, No. 4, pp. 354.
Meeting Info.: SIXTH NCI-EORTC (NATIONAL CANCER INSTITUTE-EUROPEAN ORGANIZATION FOR RESEARCH ON TREATMENT OF CANCER) SYMPOSIUM ON NEW DRUGS IN CANCER THERAPY, AMSTERDAM, NETHERLANDS, MARCH 7-10, 1989. INVEST NEW DRUGS.
CODEN: INNDDK. ISSN: 0167-6997. Language: ENGLISH.

L26 ANSWER 43 OF 47 MEDLINE on STN DUPLICATE 17
89287087. PubMed ID: 2736110. Hexadecylphosphocholine, a new ether lipid analogue. Studies on the antineoplastic activity in vitro and in vivo. Unger C; Damenz W; Fleer E A; Kim D J; Breiser A; Hilgard P; **Engel J**; Nagel G; Eibl H. (Department of Internal Medicine, University of Gottingen, West Germany.) Acta oncologica (Stockholm, Sweden), (1989) 28 (2) 213-7. Journal code: 8709065. ISSN: 0284-186X. Pub. country: Sweden. Language: English.
AB Hexadecylphosphocholine (He-PC) is a new compound synthesized according to the minimal structural requirements deducted from studies with other ether lipids. In vitro studies on He-PC revealed remarkable antineoplastic activity on HL60, U937, Raji and K562 leukemia cell lines. In addition, He-PC, applied orally, showed a superior effect in the treatment of dimethylbenzanthracene-induced rat mammary **carcinomas** when compared to intravenously administered cyclophosphamide. After oral application He-PC was well absorbed from the intestine and metabolized in the liver by phospholipases C and D. During a 5-week treatment no hematotoxic effects were detected. In a clinical pilot study on breast **cancer** patients with widespread skin involvement, topically applied He-PC showed skin **tumor** regressions without local or systemic side effects.

L26 ANSWER 44 OF 47 MEDLINE on STN DUPLICATE 18
89030924. PubMed ID: 3141197. Characterization of the **antitumor** activity of hexadecylphosphocholine (D 18506). Hilgard P; Stekar J; Voegeli R; **Engel J**; Schumacher W; Eibl H; Unger C; Berger M R. (Asta Pharma AG, Bielefeld, F.R.G.) European journal of cancer & clinical oncology, (1988 Sep) 24 (9) 1457-61. Journal code: 8112045. ISSN: 0277-5379. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Hexadecylphosphocholine (HPC) differs from ether lipids with known **antitumor** activity by its lack of the glycerol part. In the experiments described here HPC revealed outstanding **antitumor**

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activity in dimethylbenzanthracene (DMBA)-induced rat mammary **tumors**. A dose-response relationship was seen after daily oral treatment with complete suppression of **tumor** growth at doses of 46.4 mg/kg/day. There was no schedule dependence and the therapeutic efficacy was independent of the **tumor** weight at the initiation of therapy. Another autochthonous **tumor**, the benzo[a]pyrene-induced sarcoma of the rat did not respond to HPC treatment, indicating a highly selective spectrum of activity of the test compound. In comparison to an optimal single dose of cyclophosphamide, a single high dose of HPC was considerably more active against the DMBA **tumor**. At therapeutic dose levels no major toxicity of HPC was observed. Bone marrow suppression was not encountered, on the contrary, at high doses leukocytosis became apparent. The available pharmacological and toxicological data suggest that HPC may be useful in the treatment of human **cancer**.

L26 ANSWER 45 OF 47 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 19

89019248 EMBASE Document No.: 1989019248. Hexadecylphosphocholine. **Engel J.**; Schumacher W.; Hilgard P.; Stekar J.; Peukert M.; Schmahl D.; Berger M.R.; Eibl H.J.; Unger C.; Nagel G.. ASTA Pharma AG, D-6000 Frankfurt 1, Germany. Drugs of the Future 13/11 (948-951) 1988. ISSN: 0377-8282. CODEN: DRFUD4. Pub. Country: Spain. Language: English.

L26 ANSWER 46 OF 47 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1988:344814 Document No.: PREV198835039656; BR35:39656. THE **ANTITUMOR** ACTIVITY OF HEXADECYLPHOSPHOCHOLINE D-18506 IN DMBA-INDUCED RAT MAMMARY **CARCINOMAS**. HILGARD P [Reprint author]; STEKAR J; **ENGEL J** ; SCHUMACHER W; EIBL H; UNGER C; BERGER M R. ASTA PHARMA AG, D-4800 BIELEFELD 14. Proceedings of the American Association for Cancer Research Annual Meeting, (1988) Vol. 29, pp. 362.
Meeting Info.: 79TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW ORLEANS, LOUISIANA, USA, MAY 25-28, 1988. PROC AM ASSOC CANCER RES ANNU MEET.
ISSN: 0197-016X. Language: ENGLISH.

L26 ANSWER 47 OF 47 MEDLINE on STN DUPLICATE 20

89201813. PubMed ID: 3071766. Hexadecylphosphocholine (D 18506) in the topical treatment of skin metastases: a phase-I trial. Unger C; Eibl H; Breiser A; von Heyden H W; **Engel J**; Hilgard P; **Sindermann H**; Peukert M; Nagel G A. (Department of Internal Medicine, University Hospital Gottingen.) Onkologie, (1988 Dec) 11 (6) 295-6. Journal code: 7808556. ISSN: 0378-584X. Pub. country: Switzerland. Language: English.

L27	1300	FILE MEDLINE
L28	1583	FILE HCAPLUS
L29	1236	FILE EMBASE
L30	1874	FILE BIOSIS

TOTAL FOR ALL FILES

L31	5993	ENGEL, J?/AU

L32	340	FILE MEDLINE
L33	205	FILE HCAPLUS
L34	213	FILE EMBASE
L35	70	FILE BIOSIS

TOTAL FOR ALL FILES

Searched by: Mary Hale 571-272-2507 REM 1D86

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L36         828 GUNTHER, E?/AU


L37          17 FILE MEDLINE
L38          15 FILE HCAPLUS
L39          21 FILE EMBASE
L40          31 FILE BIOSIS

TOTAL FOR ALL FILES
L41          84 SINDERMANN, H?/AU

=> s l31 and l36 and l41
L42           0 FILE MEDLINE
L43           1 FILE HCAPLUS
L44           0 FILE EMBASE
L45           0 FILE BIOSIS

TOTAL FOR ALL FILES
L46           1 L31 AND L36 AND L41

=> s l46 not l25
L47           0 FILE MEDLINE
L48           0 FILE HCAPLUS
L49           0 FILE EMBASE
L50           0 FILE BIOSIS

TOTAL FOR ALL FILES
L51           0 L46 NOT L25

=> d cbib l46

L46  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
2004:120730   Document No. 140:157434  Use of alkyl phosphocholines in
     combination with antitumor medicaments for the treatment of benign and
     malignant tumors.  Engel, Jurgen; Gunther, Eckhard;
     Sindermann, Herbert (Zentaris GmbH, Germany).  PCT Int. Appl. WO
     2004012744 A1 20040212, 21 pp.  DESIGNATED STATES: W:  AU, BR, BY, CA, CN,
     CO, GE, HR, ID, IL, IN, IS, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PH, PL,
     RU, SG, UA, UZ, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE,
     CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR.
     (German).  CODEN: PIXXD2.  APPLICATION: WO 2003-EP8346 20030729.
     PRIORITY: US 2002-PV399615 20020730.


=> dis his

     (FILE 'REGISTRY' ENTERED AT 15:36:06 ON 22 SEP 2004)
               DEL HIS Y

     FILE 'REGISTRY' ENTERED AT 15:40:19 ON 22 SEP 2004
L1                STRUCTURE UPLOADED
L2                STR
L3             33 S L2
L4                STR L2
L5             33 S L4
L6          12775 S L4 FUL

     FILE 'MEDLINE, HCAPLUS, EMBASE, BIOSIS' ENTERED AT 15:50:16 ON 22 SEP 2004

     FILE 'REGISTRY' ENTERED AT 15:50:26 ON 22 SEP 2004
L7          12775 S L6 OR L6
L8           9000 S L7  RAN=(111621-46-6,)


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L9          3776 S L7  RAN=(63-89-8,111621-46-6)
L10            1 S L7  RAN=(,63-89-8)

     FILE 'MEDLINE, HCAPLUS, EMBASE, BIOSIS' ENTERED AT 15:52:18 ON 22 SEP 2004
L11         8972 FILE MEDLINE
L12        28853 FILE HCAPLUS
L13        16218 FILE EMBASE
L14        13299 FILE BIOSIS
     TOTAL FOR ALL FILES
L15        67342 S L8 OR L9 OR L10
L16          785 FILE MEDLINE
L17         2065 FILE HCAPLUS
L18         1351 FILE EMBASE
L19         1211 FILE BIOSIS
     TOTAL FOR ALL FILES
L20         5412 S L15 AND (TUMOUR? OR TUMOR? OR NEOPLASM? OR ONCOS? OR CANCER O
L21           15 FILE MEDLINE
L22           17 FILE HCAPLUS
L23           22 FILE EMBASE
L24           28 FILE BIOSIS
     TOTAL FOR ALL FILES
L25           82 S L20 AND (ENGEL, J? OR GUNTHER, E? OR SINDERMANN, H?)/AU
L26           47 DUP REM L25 (35 DUPLICATES REMOVED)
L27         1300 FILE MEDLINE
L28         1583 FILE HCAPLUS
L29         1236 FILE EMBASE
L30         1874 FILE BIOSIS
     TOTAL FOR ALL FILES
L31         5993 S ENGEL, J?/AU
L32          340 FILE MEDLINE
L33          205 FILE HCAPLUS
L34          213 FILE EMBASE
L35           70 FILE BIOSIS
     TOTAL FOR ALL FILES
L36          828 S GUNTHER, E?/AU
L37           17 FILE MEDLINE
L38           15 FILE HCAPLUS
L39           21 FILE EMBASE
L40           31 FILE BIOSIS
     TOTAL FOR ALL FILES
L41           84 S SINDERMANN, H?/AU
L42            0 FILE MEDLINE
L43            1 FILE HCAPLUS
L44            0 FILE EMBASE
L45            0 FILE BIOSIS
     TOTAL FOR ALL FILES
L46            1 S L31 AND L36 AND L41
L47            0 FILE MEDLINE
L48            0 FILE HCAPLUS
L49            0 FILE EMBASE
L50            0 FILE BIOSIS
     TOTAL FOR ALL FILES
L51            0 S L46 NOT L25

=> s l15 and (antitumor or antitumour) and (medicament? or pharmac?) and (treat? or
therap?)
L52           76 FILE MEDLINE
L53          182 FILE HCAPLUS
L54           87 FILE EMBASE
L55           56 FILE BIOSIS

TOTAL FOR ALL FILES


Searched by: Mary Hale 571-272-2507 REM 1D86
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L56         401 L15 AND (ANTITUMOR OR ANTITUMOUR) AND (MEDICAMENT? OR PHARMAC?)
                AND (TREAT? OR THERAP?)

=> s l56 and py<=2002
L57          68 FILE MEDLINE
L58         150 FILE HCAPLUS
L59          73 FILE EMBASE
L60          48 FILE BIOSIS

TOTAL FOR ALL FILES
L61         339 L56 AND PY<=2002

=> fil reg;s cisplatin/cn;s cyclophosphamide/cn ;s adriamycin/cn
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    883.80    1055.54

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     -7.70      -7.70

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DICTIONARY FILE UPDATES:  21 SEP 2004  HIGHEST RN 749178-43-6

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  conducting SmartSELECT searches.

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Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html


L62           1 CISPLATIN/CN


L63           1 CYCLOPHOSPHAMIDE/CN


L64           1 ADRIAMYCIN/CN

=> fil medline,hcaplus,embase,biosis
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     13.71    1069.25

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                      0.00      -7.70


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FILE 'MEDLINE' ENTERED AT 16:14:12 ON 22 SEP 2004

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FILE 'BIOSIS' ENTERED AT 16:14:12 ON 22 SEP 2004
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=> s (l62 or cisplatin or cyclophosphamide or l63 or adriamycin or l64) and l56
L65 8 FILE MEDLINE
L66 26 FILE HCAPLUS
L67 26 FILE EMBASE
L68 6 FILE BIOSIS

TOTAL FOR ALL FILES
L69 66 (L62 OR CISPLATIN OR CYCLOPHOSPHAMIDE OR L63 OR ADRIAMYCIN OR L64) AND L56

=> s l69 not l25
L70 6 FILE MEDLINE
L71 24 FILE HCAPLUS
L72 23 FILE EMBASE
L73 4 FILE BIOSIS

TOTAL FOR ALL FILES
L74 57 L69 NOT L25

=> dup rem l74
PROCESSING COMPLETED FOR L74
L75 55 DUP REM L74 (2 DUPLICATES REMOVED)

=> s l74 and (alkylat? agents or antimetabolites or plant alkaloid? or platinum or tumor antibiotics or (agonis? or antagonist?)(5a)natural hormones)
L76 3 FILE MEDLINE
L77 7 FILE HCAPLUS
L78 0 FILE EMBASE
L79 2 FILE BIOSIS

TOTAL FOR ALL FILES
L80 12 L74 AND (ALKYLAT? AGENTS OR ANTIMETABOLITES OR PLANT ALKALOID? OR PLATINUM OR TUMOR ANTIBIOTICS OR (AGONIS? OR ANTAGONIST?)(5A) NATURAL HORMONES)

=> dup rem l8-
L42 HAS NO ANSWERS
L44 HAS NO ANSWERS
L45 HAS NO ANSWERS
L47 HAS NO ANSWERS
L48 HAS NO ANSWERS
L49 HAS NO ANSWERS
L50 HAS NO ANSWERS
L51 HAS NO ANSWERS
L78 HAS NO ANSWERS
DUPLICATE IS NOT AVAILABLE IN 'REGISTRY'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
'80719' ANSWERS REMOVED DUE TO ANSWER OVERLAP
93397 ANSWERS REQUESTED EXCEEDS MAXIMUM ALLOWED OF 50000

Searched by: Mary Hale 571-272-2507 REM 1D86

You may process up to 50,000 answers per command. Please try to narrow your search until your resulting L# answer set is within the maximum number of answers.

=> dup rem l80
PROCESSING COMPLETED FOR L80
L81 11 DUP REM L80 (1 DUPLICATE REMOVED)

=> d 1-11 cbib abs

L81 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
2004:467712 Document No. 141:28647 Methods and compositions for drug loading in liposomes by transmembrane pH gradient. Jensen, Gerard M.; Sulivan, Michele; Yang, Stephanie; Hu, Ning (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 2004047801 A2 20040610, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US37964 20031126. PRIORITY: US 2002-PV429122 20021126.

AB A method for encapsulation of **pharmaceutical** agents (e.g., antineoplastic agents) in liposomes is provided, having preferably a high drug:lipid ratio. Liposomes can be made by a process that loads the drug by an active mechanism using a transmembrane pH gradient. Using this technique, trapping efficiencies approach 100%. Drug:lipid ratios employed are higher than for older traditional liposome prepns., and the release rate of the drug from the liposomes is reduced. After loading, residual acid is quenched with a quenching agent that is base permeable at low temps. The residual acidity is thus reduced and chemical stability (e.g. against hydrolysis) is enhanced. The stability of both the liposome and the **pharmaceutical** agent is thus maintained, prior to administration. The pH gradient is, however, present when the liposome is administered in vivo because the quenching agent rapidly exits the liposome.

L81 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
2004:467711 Document No. 141:28646 Method of drug loading in liposomes by transmembrane pH gradient. Sulivan, Michele; Yang, Stephanie; Hu, Ning; Jensen, Gerard M. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 2004047800 A2 20040610, 49 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US37790 20031126. PRIORITY: US 2002-PV429122 20021126.

AB A method for encapsulation of **pharmaceutical** agents (e.g., antineoplastic agents) in liposomes is provided, having preferably a high drug:lipid ratio. Liposomes can be made by a process that loads the drug by an active mechanism using a transmembrane pH gradient. Using this technique, trapping efficiencies approach 100%. Drug:lipid ratios employed are higher than for older traditional liposome prepns., and the release rate of the drug from the liposomes is reduced. After loading, residual acid is quenched with a quenching agent that is base permeable at low temps. The residual acidity is thus reduced and chemical stability (e.g.

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against hydrolysis) is enhanced. The stability of both the liposome and the **pharmaceutical** agent is thus maintained, prior to administration. The pH gradient is, however, present when the liposome is administered in vivo because the quenching agent rapidly exits the liposome.

L81 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
2003:833884 Document No. 139:317425 Smac-peptides as **therapeutics** against cancer and autoimmune diseases by sensitizing for TRAIL- or anticancer drug-induced apoptosis. Debatin, Klaus Michael; Fulda, Simone (Deutsches Krebsforschungszentrum Stiftung des Oeffentlichen Rechts, Germany). Eur. Pat. Appl. EP 1354952 A1 20031022, 19 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2002-8199 20020417.

AB The invention is directed to the use of Smac to sensitize different tumors and self-reactive immune cells to various pro-apoptotic stimuli, in that the cells subsequently undergo apoptosis. Therefore, Smac can be used as a compound for the manufacture of a **medicament** for the **treatment** of cancer and autoimmune diseases. Sensitization of the cells is achieved either by applying a cell-permeable form of Smac combined with known anticancer agents or by overexpression of the protein. It is an object of the invention to provide a new method in cancer and autoimmune disease **therapy** by using Smac agonists for apoptosis regulation. Thus, Smac agonists represent novel promising cancer and autoimmune disease **therapeutics** to potentiate the efficacy of cytotoxic **therapies** even in resistant tumors and immune cells. In particular, overexpression of full-length Smac protein potentiated TRAIL-induced apoptosis and also markedly increased apoptosis induced by anti-CD95 antibody or cytotoxic drugs in transfected SHEP neuroblastoma cells. The overexpression of Smac is shown to promote apoptosis through antagonizing the inhibition of XIAP of both distal and proximal events in the caspase cascade. The cytosolic Smac, with the deletion of transit peptide for mitochondria (N-terminal 55 AA), bypasses Bcl-2 inhibition in several cell types in response to different pro-apoptotic stimuli. The cell permeable Smac peptide (4 N-terminal IAP-interacting plus 3 addition following residues linked to TAT transduction domain) can facilitate intracellular delivery of Smac peptide and sensitize several resistant cell lines with defects in apoptosis signaling for **treatment** with TRAIL or doxorubicin. Expression of a cytosolic active form of Smac or cell-permeable Smac peptides bypassed the Bcl-2 block, which prevented the release of Smac from mitochondria, and also sensitized resistant neuroblastoma or melanoma cells and patient-derived primary neuroblastoma cells ex vivo. Thus, Smac agonists represent novel promising cancer **therapeutics** to potentiate the efficacy of cytotoxic **therapies**. Smac peptides is shown to enhance the **antitumor** effect of TRAIL in glioblastoma in mouse glioblastoma model and induce eradication of tumors.

L81 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
2002:521462 Document No. 137:88442 Incensole and furanogermacrens and compounds in **treatment** for inhibiting neoplastic lesions and microorganisms. Shanahan-Pendergast, Elisabeth (Ire.). PCT Int. Appl. WO 2002053138 A2 20020711, 68 pp. DESIGNATED STATES: W: AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD, UA, UG, US, VN, YU, RU, TJ, TM; RW: AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2002-IE1 20020102. PRIORITY: IE 2001-2 20010102.

AB The invention discloses the use of incensole and/or furanogermacrens, derivs. metabolites and precursors thereof in the **treatment** of neoplasia, particularly resistant neoplasia and immundysregulatory disorders. These compds. can be administered alone or in combination with

conventional chemotherapeutic, antiviral, antiparasite agents, radiation and/or surgery. Incensole and furanogermacren and their mixture showed **antitumor** activity against various human carcinomas and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.

L81 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
2000:475560 Document No. 133:109949 **Pharmaceutical** compositions for **treatment** of diseased tissues. Lee, Clarence C.; Lee, Feng-Min (USA). PCT Int. Appl. WO 2000040269 A2 20000713, 26 pp. DESIGNATED STATES: W: AU, CA, CN, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US191 20000105. PRIORITY: US 1999-PV114906 19990105.
AB A method to **treat** diseased tissue is provided where a cytotoxic compound is administered to a patient in need of **treatment** in combination with an immunostimulant. Diseased cells and/or infectious microbes/viruses are killed by the cytotoxic compound in the presence of the immunostimulant. The cell components including cellular contents and cell membrane fragments are presented by the immunostimulant to the host animal as antigens to stimulate the immune responses toward other diseased cells of the same type(s), that either remain in the vicinity or reside in distant tissues or organs. The cytotoxic mol. and immunostimulant are preferably applied locally at high concns., either sequentially or, preferably, simultaneously. For example, the composition can be administered directly to a target cancer. The composition can be prepared in various forms, such as a paste, a time release molded solid shape, a solution, a mixture with emulsifier, etc. Alternatively, the cytotoxic mol. and immunostimulant are applied in sequence.

L81 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
1998:231297 Document No. 128:248493 Encapsulation of the transition metal compounds carboplatin (CP) and lobaplatin (LP) in different types of liposomes and their physicochemical, biochemical and biological characterization. Reszka, Regina; Fichtner, Iduna; Goan, Silvia-Renate; Rudolph, Michael; Winter, Roland (Max-Delbruck-Centrum fur Molekulare Medizin, Berlin, 13122, Germany). Bioinorganic Chemistry, 145-166. Editor(s): Trautwein, Alfred X. Wiley-VCH Verlag GmbH: Weinheim, Germany. (English) 1997. CODEN: 65TRAJ.
AB The dose limiting factor in the **treatment** of head and neck as well as ovarian cancer with carboplatin and more recently lobaplatin is the myelotoxicity of both substances. In contrast, a stimulation of hematopoiesis was observed when these anticancer agents were applied to mice or rats in a specific liposomally encapsulated form. The mechanism of this hematopoietic stimulation, the **therapeutic** efficacy and the alteration of the **pharmacokinetic** behavior were investigated with respect to the lipid composition, the preparation technique, the size of the liposomes, and the interaction between the **platinum** compds. and the liposomal components. In vitro expts. were carried out to investigate the role of peritoneal macrophages in the decomposition of encapsulated carboplatin and the stimulation of cytokine release as a possible main step for the activation of the hematopoietic system. During the biophys. studies, we were not able to detect a significant perturbation or intermol. interactions of carboplatin or lobaplatin with the lipid system (1,2 Dipalmitoyl-sn-glycero-3-phosphocholine, DPPC). The in vitro **treatment** of peritoneal macrophages (mice) with carboplatin or lobaplatin encapsulated in reverse phase evaporation vesicles (REV, HEPC:CH, molar ratio 1:0.25 or 1:0.1, size distribution 0.2 to 1.5 μm) showed a stimulation of cytokines measured for instance as TNF-release. In parallel no decomposition products of carboplatin could be detected by HPLC. Following a single (i.v. or i.p.) injection, carboplatin liposomes (CPL) induced a five- or tenfold, at least 4 mo lasting increase in peripheral

white blood cells compared to the free drug in mice. A second administration in a 7-10 wk distance was able to a repeated stimulation. The colony forming activity and the percentage of cells in S-phase were elevated in spleen three days after **treatment** of mice with CPL, while these parameters remained unchanged in the bone marrow. Serum taken from CPL-**treated** nude or normal mice induced a significant colony formation of bone marrow cells in a soft agar culture. In the syngeneic ascitic murine P388 leukemia and the MethA sarcoma liposomal encapsulation resulted in a loss of **antitumor** activity. On contrary, in 3/6 solidly growing breast carcinomas, xenografted to nude mice, CPL had a superior tumor inhibiting effect compared to free carboplatin, which could be further improved by using the combination of free and liposomal drug. A combination of CPL with either **cyclophosphamide** or free carboplatin increased the **antitumor** activity and prevented the cytostatic-induced leukopenia. As mechanism for this unexpected **pharmacol.** behavior of liposomal carboplatin, we suggested, that the vesicles are taken up by the monocyte/macrophage system as their natural target. Within these cells CPL are metabolized and induce the production and release of cytokines which, secondarily, stimulate hematopoiesis. **Pharmacokinetic** data and measurements of cytokine levels in serum of **treated** mice support this hypothesis. Free carboplatin, empty liposomes or **cisplatin**-liposomes never caused a similar **pharmacol.** behavior. Lobaplatin encapsulated in REV (HEPC:CH, molar ratio 1:0.1, size distribution 0.2 to 1.5 μm) will be tested further on in vivo. First preliminary observations suggest that LPL can also stimulate the hematopoietic system.

L81 ANSWER 7 OF 11 MEDLINE on STN

93046141. PubMed ID: 1423280. Lipophilic **cisplatin** analogues entrapped in liposomes: role of intraliposomal drug activation in biological activity. Perez-Soler R; Khokhar A R. (Departmentof Medical Oncology (Section of Head, Neck, and Thoracic Medical Oncology), University of Texas M.D. Anderson Cancer Center, Houston 77030.) Cancer research, (1992 Nov 15) 52 (22) 6341-7. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB cis-Bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane **platinum** (II) (NDDP), a lipophilic **cisplatin** analogue containing two branched leaving groups of 10 carbon atoms, is undergoing clinical evaluation in a liposomal formulation. In previous studies, NDDP entrapped in multilamellar vesicles composed of dimyristoylphosphatidylcholine (DMPC) and dimyristoylphosphatidylglycerol (DMPG) at a 7:3 molar ratio was non-nephrotoxic in humans, not cross-resistant with **cisplatin** in different in vitro and in vivo systems, and more active than **cisplatin** against murine models of experimental liver metastases whereas free NDDP was devoid of in vivo **antitumor** activity at the optimal dose of L-NDDP and barely active at higher doses. To elucidate the mechanisms by which the liposomal carrier enhances the biological properties to this class of **antitumor** agents, we studied the effect of the liposome composition, size of the branched leaving groups of the **platinum** compound, and pH and composition of the aqueous phase on the entrapment efficiency, drug leakage, drug stability, and in vivo toxicity and **antitumor** activity of different liposomal formulations of these agents. In experiments using normal saline as aqueous phase, the presence of DMPG in the lipid bilayer resulted in a decreased stability and an increased biological activity of NDDP, whereas NDDP entrapped in liposomes composed of DMPC alone (not containing DMPG) was stable but devoid of **antitumor** activity. In studies with structurally related analogues with branched leaving groups of 5, 6, 7, and 9 carbon atoms, similar trends were observed. In addition, the number of carbon atoms in the leaving groups was directly and inversely related to the entrapment

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efficiency and stability of the analogues, respectively, independently of lipid composition; increasing the size of the branched leaving groups resulted in an increased in situ degradation of the **platinum** compound and enhanced biological activity and potency. These results suggest that this class of **platinum** compounds exerts its biological activity through the formation of active intermediates in situ within the lipid bilayers and that the activation reaction is highly dependent on the presence of DMPG and the size of the lipophilic leaving group.

L81 ANSWER 8 OF 11 MEDLINE on STN
92134045. PubMed ID: 1776863. Cytotoxic activity of synthetic aza alkyl lysophospholipids against drug sensitive and drug resistant human tumor cell lines. Morimoto H; Broquet C; Principe P; Mencia-Huerta J M; Braquet P; Bonavida B. (Department of Microbiology and Immunology, UCLA School of Medicine.) Anticancer research, (1991 Nov-Dec) 11 (6) 2223-9. Journal code: 8102988. ISSN: 0250-7005. Pub. country: Greece. Language: English.

AB The anti-tumor cytotoxic activity of four newly synthesized aza alkyl lysophospholipids (AALP), namely BN 52205, BN 52207, BN 52208 and BN 52211, was investigated. Using the 51Cr release assay, the four compounds were endowed with cytotoxic activity, in a concentration-dependent fashion, against various human tumor cell lines of different histological origin. Two different mechanisms appear to be involved in the AALP-mediated cytotoxicity. A rapid membrane damaging effect was observed in less than one hour's incubation of tumor cells with AALP and cytotoxicity was temperature-independent when AALP were used at greater than or equal to 200 micrograms/ml. A slower cytotoxic mechanism was observed after 18 hours incubation at 37 degrees C when AALP were used at concentrations of 30-100 micrograms/ml. The pattern and magnitube of the cytotoxic activity achieved with all the 4 AALP compounds tested were similar and the cytotoxicity mediated by combination of two compounds was additive. In addition to the cytotoxic effect, the AALP compounds also exerted a cytostatic anti-tumor effect, as assessed by inhibition of 3H TdR incorporation. Using a variety of human tumor cell lines as targets, the cytotoxic effect observed with the AALP was noted with tumor cells that were either sensitive or resistant to TNF-alpha and/or chemotherapeutic drugs such as mitomycin C, **adriamycin** and cis-**platinum**. The LD50 toxicity in mice was 100-125 mg/kg. The present findings demonstrate that AALP are cytotoxic to a variety of human tumor cell lines and do not appear to discriminate between drug/cytokine sensitive or resistant cells. Thus the present study suggests that some aza alkyl lysophospholipids may be considered as potential anticancer agents.

L81 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
1988:515934 Document No. 109:115934 Liposomes as drug carrier system for cis-diamminedichloroplatinum (II). II. **Antitumor** activity in vivo, induction of drug resistance, nephrotoxicity and **platinum** distribution. Steerenberg, P. A.; Storm, G.; De Groot, G.; Claessen, A.; Bergers, J. J.; Franken, M. A. M.; Van Hoesel, Q. G. C. M.; Wubs, K. L.; De Jong, W. H. (Lab. Pathol., Natl. Inst. Public Health Environ. Prot., Bilthoven, 3720 BA, Neth.). Cancer Chemotherapy and Pharmacology, 21(4), 299-307 (English) 1988. CODEN: CCPHDZ. ISSN: 0344-5704.

AB The use of liposomes as a drug carrier system for cis-diamminedichloroplatinum(II) (cis-DDP) was examined in order to reduce the nephrotoxicity of this drug with preservation of its **antitumor** activity. Liposomes containing phosphatidylcholine (PC)-phosphatidylserine (PS)-cholesterol (Chol) 10:1:4 were prepared using hydration media containing no or a relatively low concentration of NaCl. It was found that cis-DDP containing liposomes (lip cis-DDP) injected i.v. to IgM immunocytoma-bearing LOU/M

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rats at a dose of 1 mg cis-DDP/kg (cumulative dose 7 mg cis-DDP/kg) showed less **antitumor** activity than the free drug. The optimal cumulative dose of free cis-DDP for induction of **antitumor** activity in this tumor system is 7 mg/kg (7 + 1 mg/kg). At a dose of 2 mg lip cis-DDP/kg (cumulative dose 14 mg cis-DDP/kg) the **antitumor** activity was almost equal to that of free cis-DDP. The **antitumor** activity could not be increased by choosing another phospholipid composition of the liposomes [dipalmitoyl PC (DPPC)-dipalmitoylphosphatidylglycerol (DPPG)-Chol (10:1:10)]. Cis-DDP incorporated in DPPC-DPPG-Chol liposomes showed a similar **antitumor** activity to cis-DDP incorporated in PC-PS-Chol liposomes. After an i.v. dose of 2 mg lip cis-DDP/kg (PC-PS-Chol) kidney damage was less compared to the **treatment** with free cis-DDP (1 mg/kg). However, after a single dose of 2 mg cis-DDP/kg or a cumulative dose of 8 or 16 mg cis-DDP/kg, kidneys of rats **treated** with lip cis-DDP contained twice as much Pt as after **treatment** with free cis-DDP. Moreover, after **treatment** with lip cis-DDP, a twofold increase of the amount of Pt in tumor tissue was measured. In vitro studies with Pt recovered from spleens obtained from rats **treated** with lip cis-DDP i.v. showed that based on the equal amts. of Pt recovered the **antitumor** activity of the recovered Pt was reduced, indicating inactivation of cis-DDP in vivo. As during **treatment** with free cis-DDP, recurrence of the tumor was observed during the continued **treatment** with lip cis-DDP. It was found that these recurrent tumors were resistant to further **therapy** with cis-DDP. In conclusion, cis-DDP encapsulation into liposomes decreased the nephrotoxicity. The **antitumor** activity of cis-DDP is preserved by liposome encapsulation when it was used at a dose of 2 mg/kg, but it was reduced in terms of earlier onset of regrowth.

L81 ANSWER 10 OF 11 MEDLINE on STN DUPLICATE 1

87051340. PubMed ID: 3779646. Toxicity and **antitumor** activity of cis-bis-cyclopentenecarboxylato-1,2-diaminocyclohexane **platinum** (II) encapsulated in multilamellar vesicles. Perez-Soler R; Khokhar A R; Hacker M P; Lopez-Berestein G. Cancer research, (1986 Dec) 46 (12 Pt 1) 6269-73. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB The potential of multilamellar vesicles (MLVs) as carriers of cis-bis-cyclopentenecarboxylato-1,2-diaminocyclohexane **platinum** (II) (CPDP), a lipophilic **cisplatin** derivative, was assessed. MLVs composed of dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG), and cholesterol at different molar ratios were tested. The MLV-CPDP preparation with the highest **antitumor** activity against L1210 leukemia in vivo was DMPC:DMPG 7:3-CPDP. The encapsulation efficiency of this preparation was 66 +/- 4% (SD); the stability in 0.9% NaCl solution at 4 degrees C was 89% at 14 days and 93% 18 h after incubation in human AB serum at 37 degrees C. The toxicities of DMPC:DMPG 7:3-CPDP and free CPDP (suspended in hydroxypropyl cellulose) administered i.p. were similar (50% lethal dose = 75 versus 91 mg/kg; blood urea nitrogen values 96 h after the administration of the 50% lethal dose = 32.0 versus 34.4 mg/dl). The mean %T/C [(median survival time of **treated** mice divided by median survival time of control mice) X 100] obtained after a single i.p. injection of the optimal dose of each preparation tested was 215 (range 200 to 232) for DMPC:DMPG 7:3-CPDP, 175 (range 158 to 209) for DMPG-CPDP, 162 (range 136 to 179) for free CPDP, and 178 (range 169 to 189) for **cisplatin**. Using a multiple i.p. injection schedule (injections on Days 1, 5, and 9), DMPC:DMPG 7:3-CPDP was more active than free CPDP and **cisplatin** (%T/C: 403, 284, and 253% respectively). DMPC:DMPG 7:3-CPDP is less toxic and more active against L1210 leukemia in vivo than is **cisplatin**. The encapsulation of CPDP in MLVs composed of DMPC:DMPG 7:3 provides an adequate vehicle for the administration of this lipophilic compound and

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enhances its **antitumor** activity against L1210 leukemia.

L81 ANSWER 11 OF 11 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1987:67587 Document No.: PREV198783035913; BA83:35913. EFFECTS ON THE MONOCYTE-MACROPHAGE SYSTEM AND **ANTITUMOR** ACTIVITY AGAINST L-1210 LEUKEMIA OF CIS BISCYCLOPENTENECARBOXYLATO-TRANS-R R-1 2-DIAMINOCYCLOHEXANEPLATINUM-II ENCAPSULATED IN MULTILAMELLAR VESICLES. PEREZ-SOLER R [Reprint author]; KHOKHAR A R; CLARINGBOLD P; KASI L P; LOPEZ-BERESTEIN G. DEP CLIN IMMUNOL BIOL THERAPY, THE UNIV TEX SYST CANCER CENT, MD ANDERSON HOSP AND TUMOR INST, 6723 BERTNER AVE, HOUSTON, TX 77030, USA. Journal of the National Cancer Institute, (1986) Vol. 77, No. 5, pp. 1137-1144.
Language: ENGLISH.

AB Multilamellar vesicles (MLVs) composed of dimyristoyl phosphatidylcholine and dimyristoyl phosphatidylglycerol at a molar ratio of 7:3 were used as carriers of cis-bis-cyclopentenecarboxylato-trans-R,R-1,2-diaminocyclohexane-**platinum** (II) (CPDP). The encapsulation efficiency of liposomal CPDP (L-CPDP) was 87.6%, and its stability in normal saline at 14 days was 94.4%. The in vitro and in vivo effects on the function of the monocyte-macrophage system and the **antitumor** activity against L1210 leukemia were investigated in CD-1 and (C57BL/6J + DBA/2J)F1 mice. L-CPDP and **cisplatin** (CDDP) caused a comparable inhibition of murine-resident peritoneal macrophage (PM) protein and RNA synthesis and superoxide anion release. PM-mediated tumor cell cytotoxicity was completely inhibited at a concentration of 10 μg CDDP and L-CPDP/ml but not at concentrations of 1 and 5 μg/ml. The differences in plasma clearance of 99mTc-labeled MLV and phagocytic capacity of the liver among animals pretreated with the maximum tolerated doses of L-CPDP (25 mg/kg), empty liposomes, or CDDP (10 mg/kg) were not statistically significant (plasma clearance % of control: 105, 110, and 100, respectively: $P > .05$; liver uptake % of control: 87, 96, and 104, respectively: $P > .05$). At the maximum tolerated doses, the **antitumor** activity of L-CPDP against L1210 leukemia was similar to that of CDDP when a single dose was administered [median survival of **treated** mice/median survival of control mice + 100 (%T/C): 181 vs. 175] and slightly higher with the use of triple-dose schedule (%T/C: 275 vs. 225). L-CPDP is easy to prepare, has a high-encapsulation efficiency and stability, is not more toxic than CDDP to the monocyte-macrophage system, and is at least as effective as CDDP against L1210 leukemia.

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